

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

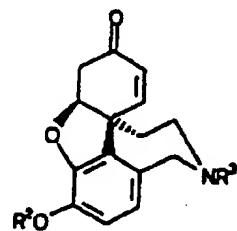
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 491/10, C12P 17/18		A1	(11) International Publication Number: WO 97/11078 (43) International Publication Date: 27 March 1997 (27.03.97)
(21) International Application Number: PCT/GB96/02335 (22) International Filing Date: 23 September 1996 (23.09.96) (30) Priority Data: 9519268.8 21 September 1995 (21.09.95) GB		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): CHIRO-SCIENCE LIMITED [GB/GB]; Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). (72) Inventors; and (73) Inventors/Applicants (for US only): BANNISTER, Robin, Mark [GB/GB]; Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE (GB). McCAGUE, Raymond [GB/GB]; 5 Mansfield Close, Milton, Cambridgeshire CB4 6EE (GB). (74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB).		Published With international search report.	

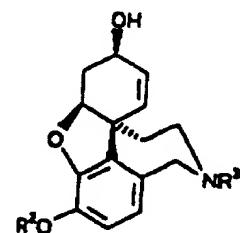
(54) Title: PROCESS FOR THE PREPARATION OF GALANTHAMINE AND ITS DERIVATIVES

(57) Abstract

A process for preparing a compound having a formula (4) or (5), in either optically-enriched or racemic form, wherein R¹, R², R³ and R⁴ are independently selected from hydrogen, alkyl, aryl, alkaryl, aralkyl and acyl groups, comprises mixing with a plant extract an oxidative cyclisation precursor of the said compound.



(4)



(5)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

PROCESS FOR THE PREPARATION OF GALANTHAMINE AND ITS DERIVATIVES

Field of the Invention

5 The present invention relates to a process for producing galanthamine and/or its derivatives from plant extracts.

Background of the Invention

10 Galanthamine (and its derivatives) are useful compounds for the treatment of Alzheimer's disease and related illnesses. Currently galanthamine, nor-galanthamine and the oxidised precursors thereof, narwedine and nor-narwedine, are usually obtained by extraction from 15 particular types of bulbs, such as daffodils or snowdrops. The yields of these extractive procedures are extremely 20 low, resulting in product(s) which are expensive and in short supply.

Studies have shown that the biosynthesis of such 25 compounds probably proceeds by a pathway similar to that shown in Scheme 1 below, where the key step is an oxidative cyclisation. These studies have also indicated that when the cyclisation precursor lacks a methyl group on the amine nitrogen (i.e. R = H) the biosynthesis to narwedine and galanthamine is disfavoured, and instead proceeds down other pathways, e.g. to pyrrolo(de)phenanthridine and 30 ethanophenanthridine alkaloids (see Barton and Kirby, J. Chem. Soc. (1961) 806 and Fuganti *et al.*, Tetrahedron Lett. (1974) 2261).

Summary of the Invention

According to the present invention, a process for 35 preparing a compound having a formula (4) or (5), in either optically-enriched or racemic form, wherein R¹, R², R³ and R⁴ are independently selected from hydrogen, alkyl, aryl, alkaryl, aralkyl and acyl groups, comprises mixing with a plant extract an oxidative cyclisation precursor of the said compound. All formulae are depicted below.

Surprisingly, the process of the present invention is capable of achieving higher yields of the desired compounds

than simple extraction from bulbs, and has the further advantage of its own simplicity. The process is particularly useful for the preparation of such compounds in optically-enriched form, more particularly (-)-galanthamine or (-)-narwediane.

Description of the Invention

Whether the process of the invention results in an optically-enriched or racemic form of a desired compound may depend upon the choice of the precursor to be mixed with the plant extract. Typically, however, an optically-enriched form is achieved. This is particularly advantageous when the product is (-)-galanthamine, or a derivative thereof, on account of its therapeutic activity. However, if the product is racemic or optically-enriched narwediane, or a derivative thereof, it can be readily converted to optically-enriched, eg. (-), galanthamine by a process such as that described by Shieh *et al*, J. Org. Chem. (1994) 59: 5463.

By optically-enriched typically we mean mixtures of enantiomers having an enantiomeric excess of at least 50%, and more typically at least 80%, or 90% or higher, thereby including single enantiomer form.

The groups R¹ to R⁴ have been defined above, and typically include up to 20 carbon atoms. The preferred precursor compound for the preparation of (-)-galanthamine has surprisingly been found to be a secondary amine having the formula (3), below, in which the nitrogen atom is unsubstituted, ie. R³ = H, contrary to what is disclosed in the prior art discussed above. Particularly preferred precursor compounds are of formula (3) in which R¹ = R³ = R⁴ = H and R² = alkyl, preferably methyl.

The plant extract is typically derived from daffodils or snowdrops, although other plants may give suitable extracts, and is preferably derived from the bulb of the plant. The extract is typically used in fragmented form, for instance by crushing with a pestle and mortar, and is then suspended in a liquid medium. Typically, the liquid

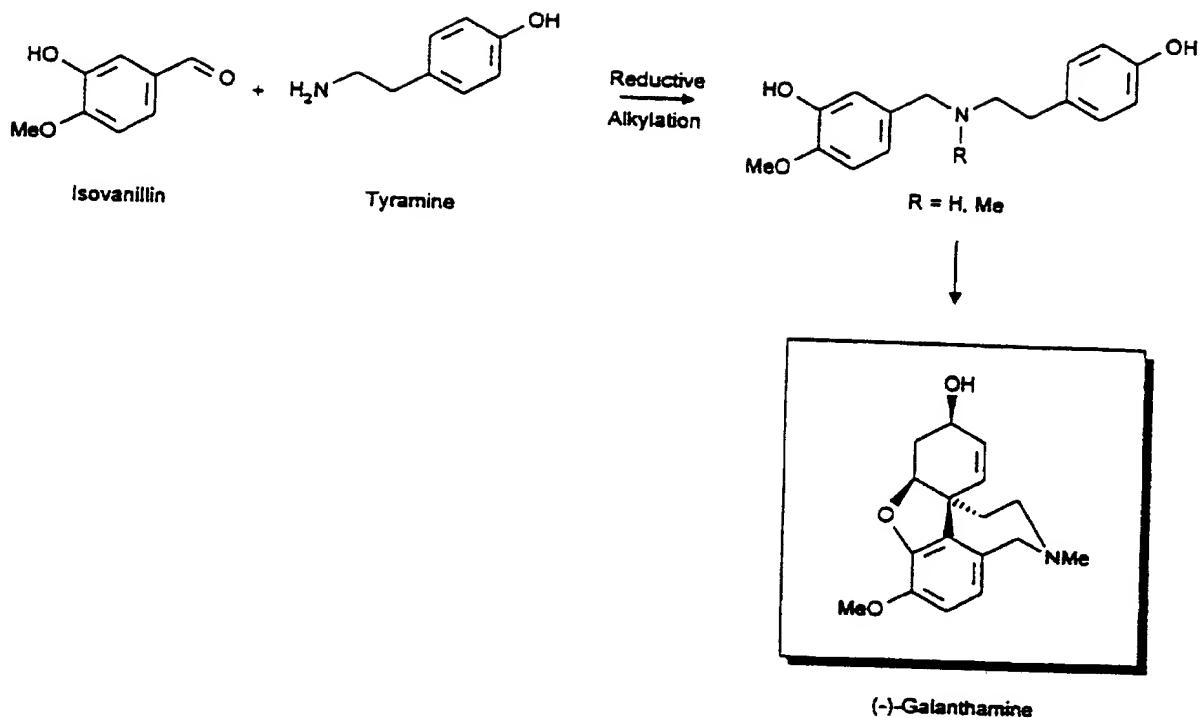
medium comprises an aqueous buffer, optionally including an additive such as an organic solvent or a surfactant. The precursor compound is then added to the liquid mixture, and preferably stirred for a period. The mixture is then 5 extracted in a conventional manner.

The present invention is now further illustrated by the following Example.

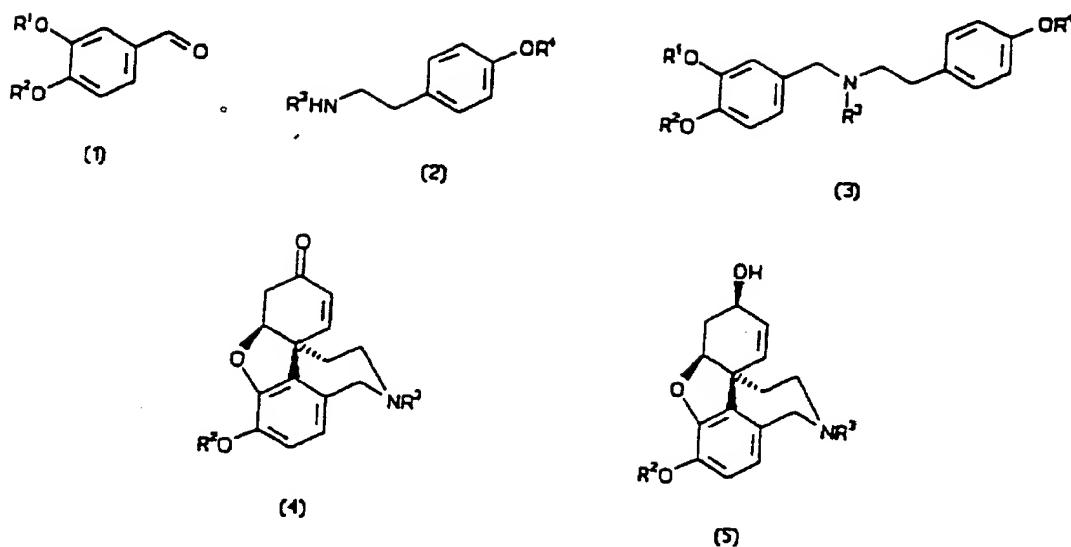
Example

Daffodil bulbs which had been stored in a refrigerator 10 were allowed to warm to room temperature over night. The bulbs were crushed with a pestle and mortar and a 1 g sample of this material was stirred with 10 mg of a secondary amine of formula (3) below, in which $R^1 = R^3 = R^4 = H$ and $R^2 = Me$, in aqueous phosphate buffer (20 ml) and 15 ethanol (10 ml) for 18 hours. The mixture was then extracted with ethyl acetate and then concentrated in vacuo. Gas chromatographic analysis of the residue indicated that three times the amount of (-)-galanthamine 20 was produced in comparison with a control reaction, which was run under identical conditions but without the addition of the amine (3).

Scheme 1



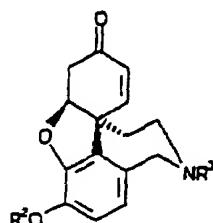
Formulae



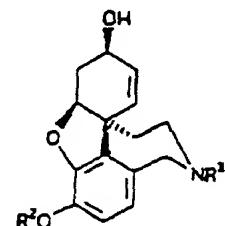
CLAIMS

1. A process for preparing a compound having a formula (4) or (5), in either optically-enriched or racemic form, wherein R¹, R², R³ and R⁴ are independently selected from hydrogen, alkyl, aryl, alkaryl, aralkyl and acyl groups, comprising mixing with a plant extract an oxidative cyclisation precursor of the said compound.

10



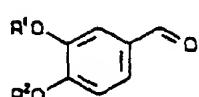
15



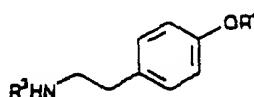
(4)

(5)

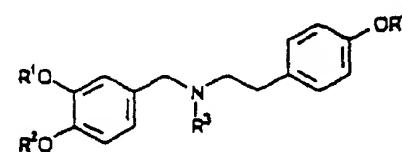
20



(1)



(2)



(3)

25

3. A process according to claim 1 or claim 2, which is for preparing the said compound in optically-enriched form.

4. A process according to claim 3, which is for preparing the said compound with the stereochemistry shown.

30 5. A process according to claim 4, which is for preparing (-)-galanthamine.

6. A process according to claim 5, wherein the precursor has the formula (3) in which R³ = H.

7. A process according to claim 6, wherein in the precursor R¹ = R⁴ = H and R² = alkyl.

35 8. A process according to claim 7, wherein R² = methyl.

9. A process according to any preceding claim, wherein the mixing is carried out in a suitable liquid medium.
10. A process according to any preceding claim, wherein the plant extract is derived from daffodils or snowdrops.
- 5 11. A process according to any preceding claim, wherein the extract is derived from the bulb of the plant.

INTERNATIONAL SEARCH REPORT

Interr. AI Application No
PCT/GB 96/02335

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/10 C12P17/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	APPLIED MICROBIOLOGY BIOTECHNOLOGY, vol. 23, no. 3-4, 1986, pages 206-210, XP000571729 G. SPASSOV ET AL: "Microbial transformations of galanthamin-precursors" see page 206 ---	1
A	LA CHIMICA E L'INDUSTRIA, vol. 51, no. 11, 1969, pages 1254-1255, XP000571896 C. FUGANTI: "Biosynthesis of galanthamine: Feeding experiments in Leucojum aestivum (Amaryllidaceae)" see page 1254 --- -/-	1

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *B* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *A* document member of the same patent family

2

Date of the actual completion of the international search

13 December 1996

Date of mailing of the international search report

20.12.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentstaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

Interr.	al Application No
PCT/GB 96/02335	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>TETRAHEDRON LETTERS, no. 26, 1974, OXFORD GB, pages 2261-2264, XP000608475</p> <p>C. FUGANTI ET AL: "Further information on the origin of the aromatic, C-6, C-1 unit of the Amaryllidaceae alkaloids" cited in the application see page 2261</p> <p>---</p>	1
A	<p>J. HETEROCYCLIC CHEM., vol. 25, - 1988 pages 1809-1811, XP000562834</p> <p>J. SZEWCZYK ET AL: "An improved synthesis of Galanthamine" see page 1809</p> <p>-----</p>	1
2		